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(54) Process for preparation of pyrazolo-(4,3-d)pyrimidin-7-ones and intermediates thereof

Verfahren zur Herstellung von Pyrazolo-(4,3-d)pyrimidin-7-ones und Zwischenprodukte davon

Procédé pour la préparation de pyrazolo-(4,3-d)pyrimidin-7-ones et leurs intermédiaires

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(56) References cited:
EP-A- 0 812 845
WO-A-98/49166
US-A- 3 992 441

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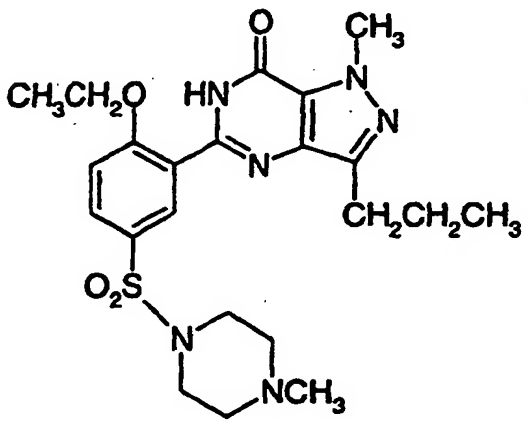
Description

[0001] This invention relates to a process for the preparation of 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine(otherwise known as sildenafil or Viagra™), and 1-Ethyl-4-{3-[3-ethyl-6,7-dihydro-7-oxo-2-(2-pyridylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenylsulphonyl}piperazine and key intermediates thereof.

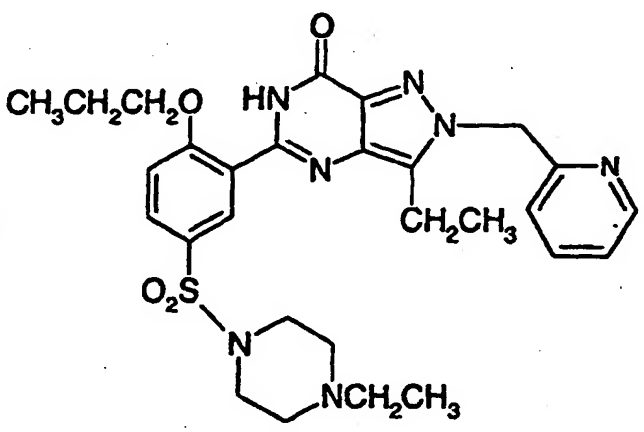
[0002] 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine (otherwise known as sildenafil) has been found to be particularly useful in the treatment of, inter alia, male erectile dysfunction (WO-A-94/28907), and a process for its preparation is disclosed in EP-A-0463756 (example 12) and Drugs of the Future 1997, 22(2): 138-143. An improved process for preparing sildenafil (over that of EP0463756) is disclosed in EP-A-0812845, with the characterising final step involving cyclisation under basic, neutral or acidic conditions to form sildenafil. A process for the preparation of 1-Ethyl-4-{3-[3-ethyl-6,7-dihydro-7-oxo-2-(2-pyridylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenylsulphonyl}piperazine is disclosed in WO 98/49166 (example 5B).

[0003] The present inventors have now found a process for preparing sildenafil and 1-Ethyl-4-{3-[3-ethyl-6,7-dihydro-7-oxo-2-(2-pyridylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenylsulphonyl}piperazine which has advantages over the aforementioned prior art processes.

[0004] According to the present invention there is provided a process for preparing a compound of formula (IA) and (IB)

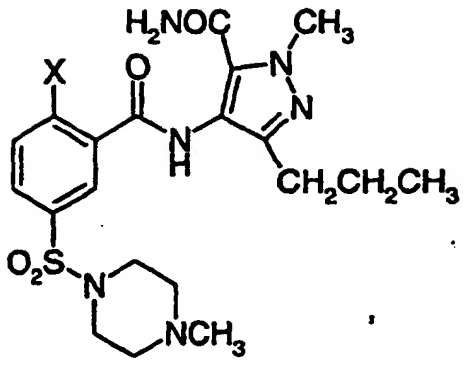


(IA)

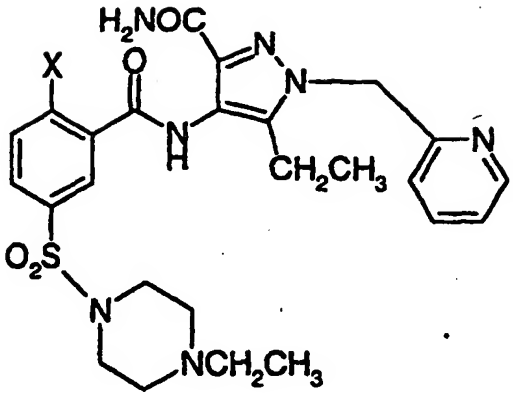


(IB)

comprising reacting a compound of (IIA) and (IIB) respectively in the presence of ^-OR, wherein R in the case of formation of compound (IA) is CH_2CH_3 and R in the case of formation of compound (IB) is $CH_2CH_2CH_3$, where X is a leaving group:



(IIA)



(IIB)

[0005] A particular advantage of the present process over that of the prior art is the elimination of steps by carrying out a substitution reaction and ring closure in 'one pot'.

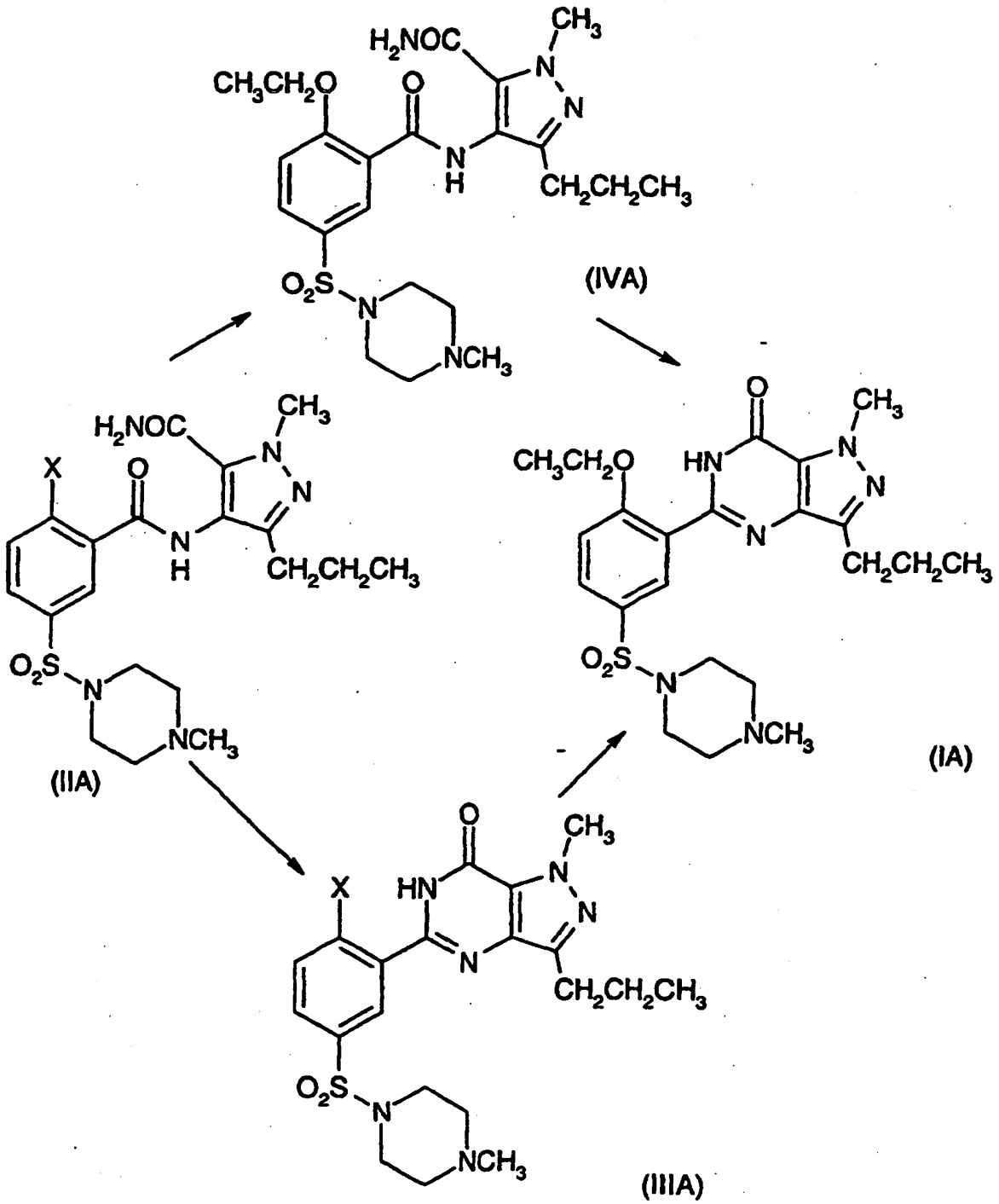
[0006] The intermediates of general formula (IIA) and (IIB) form a further aspect of the invention.

[0007] A key intermediate of the general formula (IIIA) and (IIIB) (see schemes 1 and 2 hereafter) have been identified in various reactions showing that such reactions at least partially go via a pathway of cyclisation then nucleophilic substitution. Accordingly intermediates of general formula (IIIA) and (IIIB) form yet a further aspect of the invention (wherein X is a leaving group).

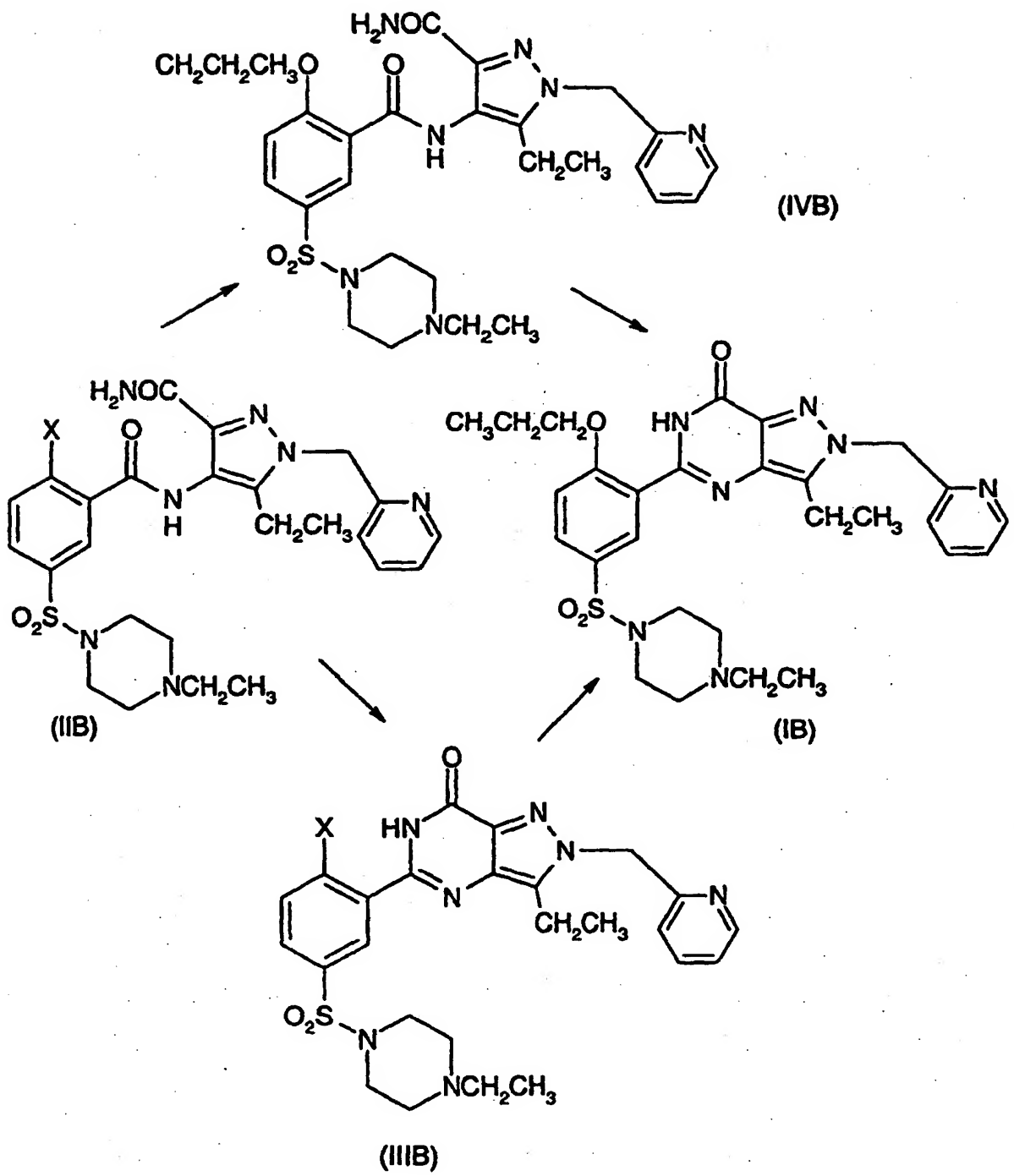
[0008] A further major intermediate of formula IVA and IVB have also been identified, suggesting that there is also nucleophilic substitution before cyclisation (and these intermediates, where novel, form a further aspect of the invention).

[0009] Thus the proposed reaction pathways for the formation of compounds (IA) and (IB) are as follows

SCHEME 1


H2NOC
CH3
CH3CH2O
O
N
N
H
CH2CH2CH3
O2S
N
NCH3
(IVA)
X
(IIA)
HN
(IA)
(IIIA)

SCHEME 2



[0010] The relative proportion of intermediates formed is partially dependent on the nature of X (the leaving group).

[0011] Leaving group X is selected from the group consisting of optionally substituted arylsulphonyloxy, preferably phenylsulphonyloxy, more preferably a para substituted aryl (phenyl) such as by a C_1-C_4 alkyl group e.g. p-toluenesulphonyloxy;

C_1-C_4 alkylsulphonyloxy e.g. methanesulphonyloxy;

nitro or halo substituted benzenesulphonyloxy preferably para substituted e.g. p-bromobenzenesulfonyloxy or p-nitrobenzenesulphonyloxy;

C_1-C_4 perfluoroalkylsulphonyloxy e.g. trifluoromethylsulphonyloxy; optionally substituted aroyloxy such as benzoyloxy;
C_1-C_4 perfluoroalkanoyloxy such as trifluoroacetyloxy;
C_1-C_4 alkanoyloxy such as acetyloxy;
halo; diazonium; methoxy; oxonium; perchloryloxy;
quaternaryammonium C_1-C_4 alkylsulphonyloxy; halosulphonyloxy e.g. fluorosulphonyloxy and other fluorinated leaving groups; halonium; and diarylsulphonylamino e.g. ditosyl (NTs_2).

[0012] Suitably X is a halo (fluoro, chloro, bromo or iodo) or methoxy, and most suitably it is fluoro or chloro. The latter have been found to provide particularly good yields, and inexpensive commercially available starting materials (chloro and fluoro benzoic acid) can readily be used.

[0013] Herein $^-OCH_2CH_3$ and $^-OCH_2CH_2CH_3$ (disclosed in the first aspect of the invention) are referred to for convenience as ^-OR. ^-OR can act as both a nucleophile (to displace the leaving group by nucleophilic substitution) and as a base (to bring about the cyclisation).

[0014] ^-OR can be generated in solution from, a salt ZOR (wherein Z is a cation) such as a metal salt. More particularly an alkali (such as sodium or potassium) or alkaline earth metal salt of ^-OR in a suitable solvent would give rise to ^-OR in solution. For example sodium ethoxide (Na^+ OEt) in a suitable solvent with intermediate (IIA) would form sildenafil. In another embodiment, ^-OR is formed insitu from ROH plus an auxiliary base (i.e. a base other than ^-OR). However, in another system, ZOR could be used in the reaction system with an auxiliary base.

[0015] Preferred embodiments of the invention are:

1. the synthesis of compound (IA) by reaction of compound (IIA):

   a) with ethanol and auxiliary base, optionally in an inert solvent;
   b) with ZOEt and an auxiliary base in ethanol or an inert solvent or both;
   c) with ZOEt and ethanol or an inert solvent or both. the synthesis of compound (IB) by reaction of compound (IIB):
   d) with propanol and auxiliary base, optionally in an inert solvent;
   e) with ZOPr and an auxiliary base, in propanol or an inert solvent or both;
   f) with ZOPr, and propanol or an inert solvent or both.

[0016] As will be appreciated the solvent in which the reaction takes place can be ROH or an inert solvent (or a mixture of both). By inert solvent we mean a solvent which will not form a nucleophile under the reaction conditions or if a nucleophile is formed it is sufficiently hindered such that it does not substantially compete in the displacement reaction. When ROH is used as a source of ^-OR, then a separate solvent is not essentially required but an (auxiliary) inert solvent (i.e. a solvent other than ROH) may be used as a co-solvent in the reaction.

[0017] Suitable solvents are as follows:

ethanol (for IA), propanol (for IB) (n-propanol), a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a tertiary C_4-C_{12} cycloalkanol, a secondary or tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine, and mixtures thereof.

[0018] A wide range of auxiliary bases can be used in the process of the invention. Typically the bases would not compete with ^-OR in the nucleophilic substitution of X (i.e.they would be non nucleophilic) by suitably being sterically hindered. Preferred bases in accordance with the invention are selected from the group consisting of metal salts of a sterically hindered alcohol or amine such as a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol and a secondary or teritary (C_3-C_8 cycloalkyl)C_1-C_6 alkanol, a N-(secondary or tertiary C_3-C_6 alkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a N-(C_3-C_8 cycloalkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a di(C_3-C_8 cycloalkyl)amine or hexamethyldisilazane;
metal salts of 1-methyl piperazine (especially for compound IA), 1-ethylpiperazine (especially for compound IB), and morpholine;
1,5-diazabicyclo[4,3,0]non-5-ene and 1,8-diazabicyclo[5,4,0]undec-7-ene; tertiary amines such as triethylamine; metal hydride, oxide, carbonate, and bicarbonate.

[0019] Preferably the metal of the salt of ZOR and the auxiliary base are independently selected from alkali metals (lithium, sodium, potassium, rubidium, caesium) or alkaline earth metals (beryllium, magnesium, calcium, strontium, barium). More preferably the metal is sodium or potassium.

[0020] Preferably the auxiliary base is selected from the group consisting of metal salts of a sterically hindered alcohol or amine such as a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol and a secondary or tertiary (C_3-C_8

cycloalkyl)C_1-C_6 alkanol, a N-(secondary or tertiary C_3-C_6 alkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a N-(C_3-C_8 cycloalkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a di(C_3-C_8 cycloalkyl)amine or hexamethyldisilazane; 1,5-diazabicyclo[4,3,0]non-5-ene and 1,8-diazabicyclo[5,4,0]undec-7-ene; metal hydride, oxide, carbonate and bicarbonate.

[0021] More preferably still, the auxiliary base is selected from the sterically hindered bases of the previous paragraph (i.e. all of them except the metal hydride, oxide, carbonate and bicarbonate).

[0022] Most preferably the auxiliary base is the metal salt of a tertiary C_4-C_6 alcohol such as the alkali or alkaline earth metal salts (e.g. Na/K) of t-butanol or t-amyl alcohol.

[0023] To maximise yields, it is further preferred that at least one molecular equivalent (suitably one and a half equivalent) of auxiliary base and ^-OR are used in accordance with the invention. If ^-OR also functions as a base then preferably at least two equivalents, (more preferably three equivalents) of ^-OR are present. Thus for example in preferred embodiments (a) to (f) above, preferably there is at least 2 equivalents of auxiliary base and at least one equivalent of EtOH or PrOH (a and d respectively), preferably at least 1 equivalent of auxiliary base and at least 1 equivalent of ZOEt or ZOPr (b and e respectively) and preferably at least 2 equivalents of ZOEt or ZOPr (c and f respectively). These are equivalents with respect to the molar quantities of IIA or IIB.

[0024] The nature of the leaving group (X) may influence the reaction pathway. For example with reference to scheme 1 for compound (IA), when X = F the reaction mostly proceeds via the intermediate illustrated by (IVA) but when the X = Cl the pathway shifts more towards the intermediate of (IIIA), and when X = OCH_3 there is more of the formula (IIIA) intermediate formed than the formula (IVA) type intermediate. However, formation of the final compound of formulae (IA) and (IB) from the intermediate formulae (IIIA) and (IIIB) respectively can be encouraged by using a higher temperature and allowing more time for formation of the final product.

[0025] Preferably the general reaction is carried out at from 50°C to 170°C. Thus where X=F, the reaction temperature could be anything from about 50°C, preferably 60°C upward and the rate of formation of the final product would be very good. For X=Cl, preferably a temperature of 60 to 170°C, more suitably at least 80°C such as (80°C to 110°C) would increase the rate; and for X=OCH_3, preferably a temperature of at least 80°C, more suitably at least 110°C (such as 110°C to 140°C) would increase the rate to the final product.

[0026] The compounds of general formula (IIA) and (IIB) may be obtained from readily available starting materials for example, by the route depicted in the following reaction schemes. Reaction scheme 3 is illustrated for compound (IA) and scheme 4 is illustrated for compound (IB).

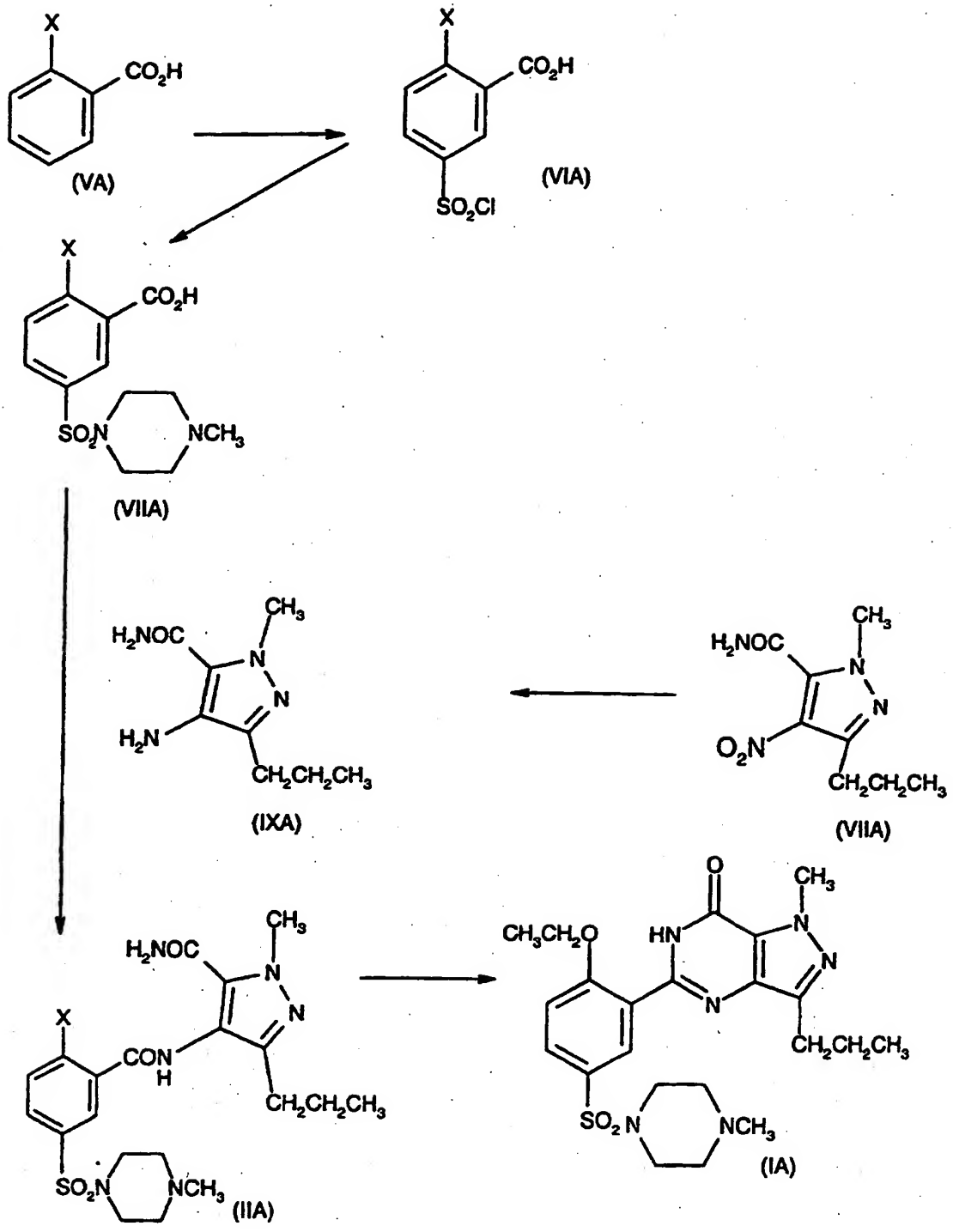
[0027] With reference to scheme 3, the intermediate of formula (VIA) is formed from a substituted (i.e. group X) benzoic acid derivative by reaction with chlorosulphonic acid. Intermediate (VIA) is then reacted with N-methylpiperazine in the presence of a base, such as a tertiary amine, more particularly triethylamine and a suitable solvent such as acetone or water to form intermediate (VIIA).

[0028] (IIA) is formed by reaction of intermediate (VIIA) and 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (compound IXA) in the presence of a coupling agent, such as 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride and where desirable also in the presence of a base and/or an accelerator. In one example of a coupling system, the carboxylic acid function of (VIIA) is first of all activitated using about a 5% excess of a reagent such as N,N'-carbonyldimidazole (as coupling agent) in a suitable solvent, e.g. ethyl acetate, at from about room temperature to about 80ºC, followed by reaction of the intermediate imidazolide with (IXA) at from about 20 to about 60ºC. In another example, intermediate (VIIA) could be coupled to the pyrazole (IXA) in the presence of 1-hydroxybenzotriazole, triethylamine and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride.

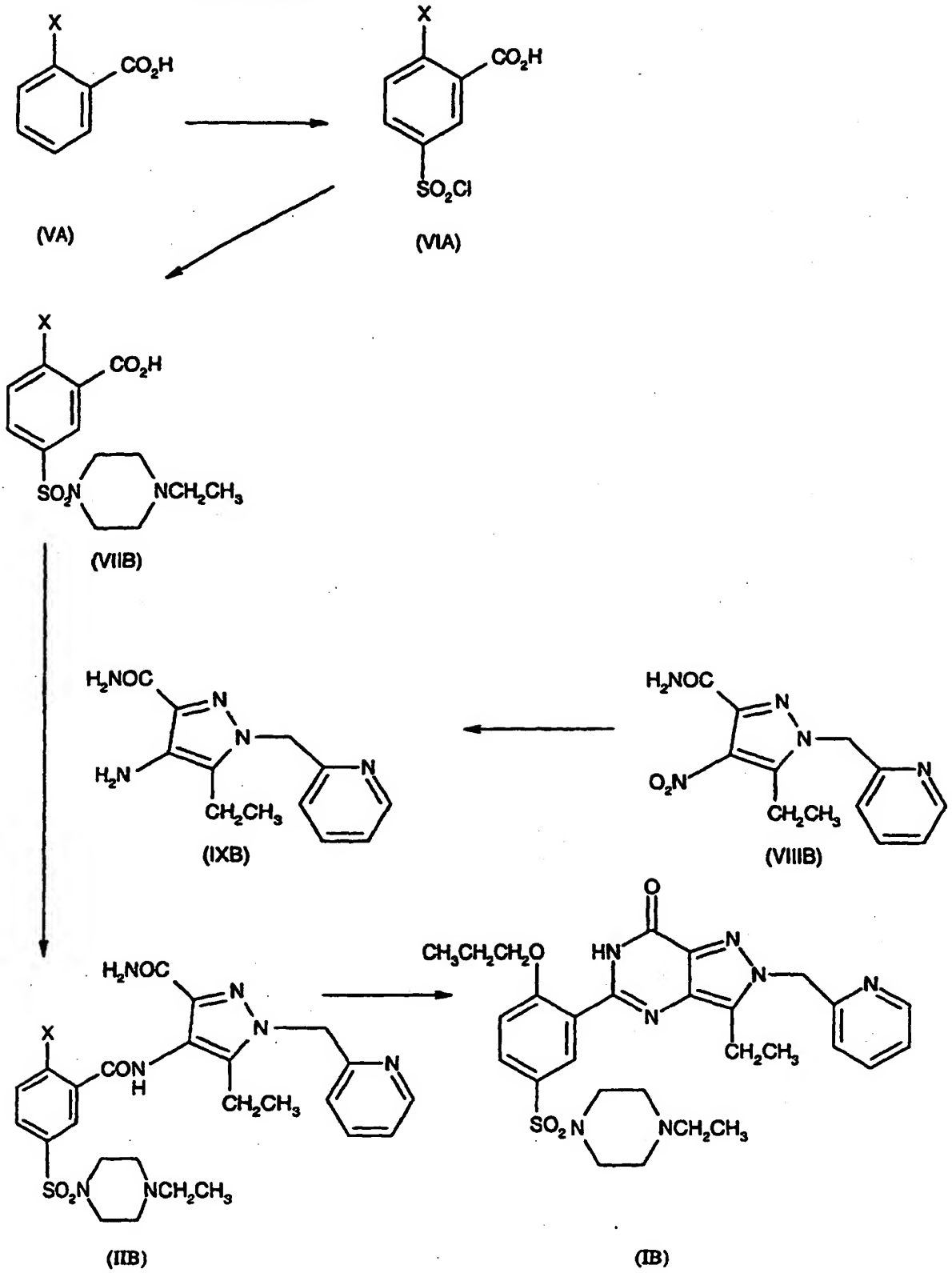
[0029] Compound (IXA) is formed by reducing 1-methyl-4 nitro-3-propyl-1H-pyrazole-5 carboxamide (VIIA) such as by hydrogenation in the presence of 5% palladium on charcoal.

[0030] Compound (IB) (scheme 4) can be formed in an analogous fashion to that of compound (IA). More particularly, intermediate (VIIB) is prepared by reacting (VIA) with N-ethylpiperazine; and intermediate (IIB) is formed by coupling intermediate compounds (VIIB) and (IXB).

SCHEME 3


X
CO2H
(VA)
X
CO2H
SO2Cl
(VIA)
X
CO2H
SO2N
NCH3
(VIIA)
CH3
H2NOC
N
N
H2N
CH2CH2CH3
(IXA)
CH3
H2NOC
N
N
O2N
CH2CH2CH3
(VIIA)
CH3
H2NOC
N
N
X
CON
H
CH2CH2CH3
SO2N
NCH3
(IIA)
O
CH3
CH3CH2O
HN
N
N
CH2CH2CH3
SO2N
NCH3
(IA)

SCHEME 4



[0031] The intermediates of general formulae (VIIA) and (VIIB) are novel and form a further aspect of the invention (wherein X is as defined hereinbefore)

[0032] The invention will now be described by way of example only with reference to the following examples.

Example 1:

(1a) 5-Chlorosulphonyl-2-fluorobenzoic acid (Compound VIA, X=F)

[0033] Commercially available 2-fluorobenzoic acid (75g, 0.54Mol) was added to chlorosulphonic acid (320g) over 15 minutes, stirred for 30 minutes then heated to 90ºC for 4½ hrs. Once cool, the reaction was quenched onto ice/water (1.5kg/324ml) and granulated for 1 hr. The precipitated product was filtered, water washed and dried at 50ºC under vacuo to give the title compound (99.7g, 78.1%) as a white solid.

(1b) 2-Fluoro-5-(4-methyl-1-piperazinylsulphonyl)benzoic acid Compound VIIA, X=F)

[0034] A solution of 5-chlorosulphonyl-2-fluorobenzoic acid (47.72g, 0.2mol) in acetone (250ml) was added to a mixture of N-methylpiperazine (22.04g, 0.22mol) and triethylamine (24.29g, 0.24mol) and the reaction was stirred at ambient for three hours. The mixture was filtered, the resulting solid was recrystallised from water to afford the title compound (14.63g, 24.2%) as a white solid. δ (DMSO): 2.30 (3H, s), 2.58 (4H, m), 2.95 (4H, m), 7.52 (1H, m), 7.90 (1H, m), 8.10 m/z (Found: 303 $[M+H]^+$, 100%, $C_{12}H_{16}FN_2O_4S$ requires 303).

(1c) 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide

[0035] A stirred suspenson of 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxamide (EP-A-0463756; 237.7 g, 1.12 mol) and 5% palladium on charcoal (47.5 g) in ethyl acetate (2.02 1) was hydrogenated at 344.7 kPa (50 psi) and 50ºC for 4 hours, when the uptake of hydrogen was complete. The cool reaction mixture was filtered, then the filter pad washed with ethyl acetate, the combined filtrate and washings thus furnishing an ethyl acetate solution of the title compound (EP-A-0463756) which was of sufficient purity to use directly in the next stage of the reaction sequence.

(1d) 4-[2-Fluoro-5-(4-methyl-1-piperazinylsulphonyl)benzamido]-1-methyl-3-propyl-1H-pyrazole-5-carboxamide. (Compound IIA, X=F)

[0036] 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (1.27g, 6.94 mmol) was added to a suspension of 2-fluoro-5-(4-methyl-1-piperazinylsulphonyl)benzoic acid (2.0g, 6.94mmol), triethylamine (0.70g, 6.92mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.33g, 6.94mmol) and 1-hydroxybenzotriazole (0.94g, 6.96mmol) in a mixture of ethyl acetate (20ml) and dichloromethane (20ml). The reaction mixture was stirred for 12 hours at ambient temperature. The reaction mixture was stripped down to an oil and purified using column chromatography (flash silica, 30:70, methanol:ethyl acetate). The title compound of preparation was further purified by dissolving in dichloromethane and washing with saturated sodium bicarbonate solution. The organic solution was stripped down under vacuum to produce a solid which was dried (40°C) to afford the title compound (2.1 g, 64.8%) as a white solid.
m.p. 210-212°C. Found: C.51.15; H, 5.81; N, 17.90. $C_{20}H_{27}FN_6O_4S$ requires C, 51.49; H, 5.83; N, 18.01. δ ($CDCl_3$) : 0.95 (3H, t), 1.62 (2H, m), 2.30 (3H, s), 2.50 (6H, m), 3.10 (4H, m), 4.10 (3H, s), 7.41 (1H, m), 8.00 (2H, m), 8.50 (1H, m). m/z (Found: 467.18909 ($[M+H]^+$, 37%), $C_{20}H_{28}N_6O_4SF$ requires 467.1890).

(1e) 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine. (Compound IA)

[0037] Potassium *t*-butoxide (0.74g, 6.60mmol) was added to a suspension of the title compound of example (1d) (1.00g, 2.20mmol) in ethanol (5ml) and the mixture was heated under reflux for 48 hours. The reaction mixture was stripped down to an oil and purified by dissolving in dichloromethane and washing with saturated sodium bicarbonate solution. Hexane was added to the organic solution over 10 minutes, a precipitated solid filtered and dried to afford the title compound (1.1g,100%) as a white solid. Recrystallisation of the title compound from ethyl acetate affords a solid with m.p.184-186°C. Found: C, 55.49; H, 6.35; N, 17.72. $C_{22}H_{31}N_6O_4S$ requires C, 55.58; H, 6.53; N, 17.68. δ (DMSO): 0.96 (3H, t), 1.30 (3H, t), 1.72 (2H, m), 2.13 (3H, s), 2.36 (4H, m), 2.72 (2H, t), 2.90 (4H, m), 4.18 (5H, m), 7.32 (1H, d), 7.80 (2H, m). m/z (Found: 475.214800 ($[M+H]^+$, 100%). $C_{22}H_{31}N_6O_4S$. requires 475.212751).
[0038] The reaction went almost entirely via intermediate IVA, and went to completion in less than 48 hours.

Example 2:

(2a) 2-Chloro-5-chlorosulphonylbenzoic acid (compound VIA, X=Cl)

[0039] Commerically available 2-chlorobenzoic acid (80.0g), (0.5mol), was added portionwise to chlorosulphonic acid (320g) with vigorous stirring. The reaction was heated to 95ºC for 6hrs then cooled overnight to room temperature. The solution was quenched onto ice/water (1.5kg/324 ml) and stirred for 15min. The precipitated product was filtered, water washed and dried at 50ºC in vacuo, to give the title compound (111.1g, 85.2%) as a white solid with m.p. 140°C. δ ($CDC1_3$): 7.42 (1H,m), 8.27 (1H,m), 8.75 (1H,m).

(2b) 2-Chloro-5-(4-methyl-1-piperazinylsulphonyl)benzoic acid (Compound VIIA, X=Cl)

[0040] The above compound was prepared by adding 2-chloro-5-chlorosulphonylbenzoic acid to 1.25 mol equivalent of N-ethylpiperazine in water (3ml/g) under acidic conditions.

[0041] The title compound was then isolated as a solid (81.7%). Recrystallisation of the title compound from acetone: water affords a solid with m.p. 304-6ºC, and the following characteristic data:

Found: C, 45.16; H, 4.71; N, 8.64. $C_{12}H_{15}ClN_2O_4S$ requires C, 45.21; H, 4.71; N, 8.79. δ (DMSO): 2.20 (3H, s), 2.50 (4H, m), 2.95 (4H, m), 6.75 (2H, m), 9.95 (1H, s), m/z (Found: 319 $[M+H]^+$, 100% $C_{12}H_{16}ClN_2O_4S$ requires 319).

(2c) 4-[2-Chloro-5-(4-methyl-1-piperazinylsulphonyl)benzamido]-1-methyl-3-propyl-1H-pyrazole-5-carboxamide. (Compound IIA, X=Cl)

[0042] 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (2.86g, 15.68mmol) (example 1c) was added to a suspension of 2-chloro-5-(4-methyl-1-piperazinylsulphonyl)benzoic acid (5.0g, 15.68mmol), triethylamine (1.59g, 15.68mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.00g, 15.68mmol), and 1-hydroxybenzotriazole (2.12g, 15.68mmol) in dichloromethane (50ml). The reaction was stirred for 48 hours at ambient temperature, a further portion of 1-(3-dimethylaminopropyl)-3-ethyl carbodimide hydrochloride (1.00g, 5.2mmol) added and the reaction stirred for a further 48 hours at ambient temperature. The reaction mixture was washed with saturated sodium bicarbonate solution and ethyl acetate added to the separated organic solution over ten minutes. The mixture was stirred for ten minutes and a precipitated solid filtered, and dried to afford the title compound (6.0g, 81%). m.p 105-107°C . δ (DMSO): 0.90 (3H, t), 1.60 (2H, m), 2.13 (3H, s), 2.40 (4H, m), 2.50 (2H, m), 2.95 (4H, m), 3.90 (3H, s), 7.30 (1H, s), 7.82 (4H, m), 10.0 (1H, s). m/z (Found: 505.140303 ($[M+Na]^+$, 28%). $C_{20}H_{27}ClN_6O_4SNa$. requires 505.140073).

(2d) 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine. (Compound IA)

[0043] Potassium *t*-butoxide (1.43g, 12.75mmol) was added to a suspension of the title compound of example 2(c) (2.00g, 4.25mmol) in ethanol (20ml) and the mixture was heated under reflux for 48 hours. The pH of the reaction was adjusted to 6, using 1N hydrochloric acid, the precipitated solid filtered and dried to afford the title compound. Recrystallisation of the title compound from methyl isobutyl ketone afforded a solid with m.p 188°C. δ ($CDCl_3$): 1.01 (3H, t), 1.62 (3H, t), 1.88 (2H, m), 2.30 (3H, s), 2.50 (4H, m), 2.95 (2H, t), 3.13 (4H, m), 4.30 (3H, s), 4.39 (2H, q) 7.15 (1H, d), 7.82 (1H, m), 8.82 (1H, m). m/z (Found: 475.2127 ($[M+H]^+$, 100%). $C_{22}H_{31}N_6O_4S$. requires 475.212751).

[0044] Intermediate of formula IVA was prepared in accordance with EP-A-0812845, and intermediate of formula IIIA, X=Cl was prepared in accordance with example 2(e) herebelow. These intermediates were then used as markers for comparison of hplc samples taken from the reaction mixture during step 2(d), in order to deduce the reaction path.

[0045] Intermediates IIIA (X=Cl) and IVA were observed (by hplc) in a ratio of about 20:80 respectively.

2(e): 1-[4-Chloro-3-(6,7-dihydro-1-methyl-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]-4-methylpiperazine, (Compound IIIA, X=Cl)

[0046] Potassium *t*-butoxide (0.24g, 2.14mmol) was added to a suspension of the title compound of example 2(c) (1.00g, 2.12mmol) in t-butanol (5ml) and the mixture was heated under reflux for 120 hours. The reaction mixture was cooled and the precipitated solid was filtered and dried to afford the title compound (0.48g, 50%) as a white solid m. p. 205-208°C. δ (DMSO): 0.90 (3H, t), 1.70 (2H, m), 2.13 (3H, s), 2.38 (4H, m), 2.68 (2H, t), 2.92 (4H, m), 4.10 (3H, s), 4.15 (1H, s), 7.60 (1H, m), 7.70 (1H, d), 7.85 (1H, m). m/z (Found: 465.1484 ($[M+H]^+$, 100%). $C_{20}H_{26}ClN_6O_3S$

requires 465.147564).

Example 3:

(3a) 5-Chlorosulphonyl-2-methoxybenzoic acid (Compound VIA, X=OCH_3)

[0047] Commercially available 2-methoxybenzoic acid (15.2g, 0.1 mol) was added portionwise to chlorosulphonic acid (52.43g) over 30min with ice cooling. Thionyl chloride (11.9g, 0.1 mol) was added and the reaction stirred overnight. The reaction was quenched onto ice/water (250g/65ml) and the precipitated product granulated for 1hr, filtered, water washed and oven dried to give the title compound (23.56g, 93.9%) as a white solid with m.p. 138-140°C. δ ($CDCl_3$): 4.18 (3H, s), 7.23 (1H, d), 8.21 (1H, d), 8.78 (1H, s).

(3b) 2-Methoxy-5-(4-methyl-1-piperazinylsulphonyl)benzoic acid

[0048] The above compound was prepared by adding 5-chlorosulphonyl-2-methoxybenzoic acid to 1.1 mol equivalent of N-methylpiperazine and 1.2 mol equivalents of triethylamine in acetone (5ml/g).

[0049] The title compound was then isolated by filtration, as a solid (79.1%), with the following characteristic data:

Found: C, 49.70; H, 5.76; N, 8.75. $C_{13}H_{18}N_2O_5S$ requires C, 49.68; H, 5.73; N, 8.92. δ (DMSO): 2.15 (3H, s), 2.35 (4H, m), 2.90 (4H, m), 3.90 (3H, s), 7.25 (1H, m), 7.10 (2H, m), m/z (Found: 315 $[M+H]^+$, 65% $C_{13}H_{19}N_2O_5S$ requires 315).

(3c) 4-[2-Methoxy-5-(4-methyl-1-piperazinylsulphonyl)benzamido]-1-methyl-3-propyl-1H-pyrazole-5-carboxamide. (Compound IIA, X=OCH_3)

[0050] A mixture of 2-methoxy-5-(4-methyl-1-piperazinylsulphonyl)benzoic acid (2.00g, 6.36mmol) and carbonyl diimidazole (1.03g,6.35mmol) in dichloromethane (20ml) was stirred for three hours at 30°C. 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (1.16g, 6.37mmol) and triethylamine (0.64g, 6.32mmol) were added to the reaction mixture and stirred for 48 hours at ambient temperature. The reaction mixture was washed with saturated sodium bicarbonate solution, the separated organic solution stripped under vacuum to produce a solid which was dried (40 °C) to afford the title compound (2.74g, 90%) as a white solid. m.p. 182°C. Found: C, 52.42; H, 6.36; N, 17.31; $C_{21}H_{30}N_6O_5S$ requires C, 52.71; H, 6.32; N, 17.56. δ (DMSO): 0.90 (3H, t), 1.60 (2H, m), 2.12 (3H, s), 2.32 (4H, m), 2.42 (2H, t), 2.90 (4H, m), 3.90 (3H, s), 4.00 (3H, s), 7.32 (1H, s) 7.42 (1H, d), 7.80 (1H, s), 7.90 (2H, m), 9.70 (1H, s). m/z (Found: 479.2088 ($[M+H]^+$, 52%). $C_{21}H_{31}N_6O_5S$. requires 479.207665).

3d) 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine. (Compound IA)

[0051] Potassium-*t*-butoxide (146mg,1.30mmol) was added to a suspension of the title compound of step 3c (200mg, 0.43mmol) in ethanol (4ml) and the mixture was heated under reflux for 120 hours. The reaction mixture was cooled and the pH of the reaction was adjusted to 6, using dilute hydrochloric acid. The precipitated solid was filtered and dried to afford the title compound (60mg, 29%) as an off white solid with m.p. 187°C. δ ($CDCl_3$): 1.00 (3H, t), 1.62 (3H, t), 1.90 (2H, m), 2.22 (3H, s), 2.50 (4H, m), 2.95 (2H, t), 3.10 (4H, m), 4.30 (3H, s), 4.38 (2H, q), 7.15 (1H, d), 7.82 (1H, d), 8.82 (1H, s), 10.85 (1H, s). m/z (Found: 497.199635 [M^+, 100%]. $C_{22}H_{30}N_6O_4S$. requires 497.194695).

[0052] The following intermediate 3(e) was independently prepared and used as a marker for hplc comparison of samples taken from the reaction mixture during step 3(d).

[0053] The intermediate of example 3(e) (IIIA, X=OCH_3) and intermediate IVA were observed by hplc in a ratio of about 70:30 respectively.

(3e) 1-[3-(6,7-Dihydro-1-methyl-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)4-methoxy-phenylsulphonyl]-4-methylpiperazine (Compound IIIA, X=OCH_3)

[0054] Potassium *t*-butoxide (0.176g, 1.57mmol) was added to a suspension of the title compound of step 3c (0.75g, 1.57mmol) in t-butanol (5ml) and the mixture was heated under reflux for 96 hours. The reaction mixture was cooled and the precipitated solid was filtered and dried to afford the title compound (0.33g, 45.6%) as a white solid m.p. 182°C. δ ($CDCl_3$): 1.02 (3H, t), 1.88 (2H, m), 2.30 (3H, s), 2.50 (4H, m), 2.92 (2H, t), 3.10 (4H, m), 4.15 (3H, s), 4.30 (3H, s), 7.20 (1H, m), 7.95 (1H, d), 8.10 (1H, m).

Example 4:

(4a) Ethyl 3-ethyl-1H-pyrazole-5-carboxylate

[0055] Ethanolic sodium ethoxide solution (21% w/w; 143 ml, 0.39 mol) was added dropwise to a stirred, ice-cooled solution of diethyl oxalate (59.8 ml, 0.44 mol) in absolute ethanol (200 ml) under nitrogen and the resulting solution stirred for 15 minutes. Butan-2-one (39 ml, 0.44 mol) was then added dropwise, the cooling bath removed, the reaction mixture stirred for 18 hours at room temperature and then for 6 hours at 40°C, then the cooling bath reintroduced. Next, glacial acetic acid (25 ml, 0.44 mol) was added dropwise, the resulting solution stirred for 30 minutes at 0°C, hydrazine hydrate (20 ml, 0.44 mol) added dropwise, then the reaction mixture allowed to warm to room temperature and maintained there over a period of 18 hours, before being evaporated under reduced pressure. The residue was partitioned between dichloromethane (300 ml) and water (100 ml), then the organic phase separated, washed with water (2 x 100ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound (66.0 g). δ ($CDCl_3$): 1.04 (3H,t), 1.16 (3H,t), 2.70 (2H,q), 4.36 (2H,q), 6.60 (1H,s). LRMS: m/z 169 $(M+1)^+$.

(4b) 3-Ethyl-1H-pyrazole-5-carboxylic acid

[0056] Aqueous sodium hydroxide solution (10M; 100 ml, 1.0 mol) was added dropwise to a stirred suspension of the title compound of example (4a) (66.0 g, 0.39 mol) in methanol and the resulting solution heated under reflux for 4 hours. The cool reaction mixture was concentrated under reduced pressure to ca. 200 ml, diluted with water (200 ml) and this mixture washed with toluene (3 x 100 ml). The resulting aqueous phase was acidified with concentrated hydrochloric acid to pH 4 and the white precipitate collected and dried by suction to provide the title compound (34.1 g). δ ($DMSO_{d6}$): 1.13 (3H,t), 2.56 (2H,q), 6.42 (1H,s).

(4c) 3-Ethyl-4-nitro-1H-pyrazole-5-carboxylic acid

[0057] Fuming sulphuric acid (17.8 ml) was added dropwise to stirred, ice-cooled fuming nitric acid (16.0 ml), the resulting solution heated to 50°C, 3-ethyl-1H-pyrazole-5-carboxylic acid added portionwise over 30 minutes whilst maintaining the reaction temperature below 60°C. The resulting solution was heated for 18 hours at 60°C, allowed to cool, then poured onto ice. The title compound was obtained as a brown solid (64%). δ ($DMSO_{d6}$): 1.18 (3H,t), 2.84 (2H,m), 13.72 (1H,s).

(4d) 3-Ethyl-4-nitro-1H-pyrazole-5-carboxamide

[0058] A solution of the title compound of example (4c) (15.4 g, 0.077 mol) in thionylchloride (75 ml) was heated under reflux for 3 hours and then the cool reaction mixture evaporated under reduced pressure. The residue was azeotroped with tetrahydrofuran (2 x 50 ml) and subsequently suspended in tetrahydrofuran (50 ml), then the stirred suspension ice-cooled and treated with gaseous ammonia for 1 hour. Water (50 ml) was added and the resulting mixture evaporated under reduced pressure to give a solid which, after trituration with water and drying by suction, furnished the title compound as a white solid (90%). δ ($DMSO_{d6}$): 1.17 (3H,t), 2.87 (2H,m), 7.40 (1H,s), 7.60 (1H,s), 7.90 (1H, s). LRMS: m/z 185 $(M+1)^+$.

(4e) 5-Ethyl-4-nitro-1-(2-pyridylmethyl)-1H-pyrazole-3-carboxamide. (Compound VIIIB)

[0059] Caesium carbonate (1.414 kg, 4.34mol) was added to a suspension of the title compound of example (4d) (800g, 4.34mol) in acetonitrile (5l) and the mixture warmed to 60°C. 2-Chloromethylpyridine (664.7g, 5.23mol) was added and the reaction heated at 70°C for 7 hours, then water (9.5l) added and the reaction mixture cooled to 10°C. Granulation of this mixture gave a precipitate which was filtered and dried to afford 3-ethyl-4-nitro-1-(pyridin-2-yl)methyl-pyrazole-5-carboxamide (367g). Sodium chloride (1.58 kg) was added to the filtrate and the solution extracted with ethyl acetate (4 x 1.75l). The combined organic extracts were distilled to remove approximately 10 l of solvent, toluene (5.6l) added over 35 minutes to the hot (69-76°C) solution and the mixture allowed to cool. The resulting suspension was granulated at <10°C for 30 minutes, filtered, the solid washed with ethyl acetate:toluene (50:50) 600 ml) and dried (60°C) to afford the title compound (624g 52%) as a light brown solid. δ ($DMSO_{d6}$): 1.08 (3H,t), 3.02 (2H,q), 5.53 (2H, s), 7.34 (2H,m), 7.65 (1H,s), 7.82 (1H,m), 7.93 (1H,s), 8.52 (1H,d). LRMS: m/z 276 $(M+1)^+$.

(4f) 4-Amino-5-ethyl-1-(2-pyridylmethyl)-1H-pyrazole-3-carboxamide. (Compound IXB)

[0060] A mixture of Lindlar catalyst (2g) and the title compound of example (4e) (20g, 72.7mmol) in ethanol (160ml)

was hydrogenated for 48 hours at 345kPa (50psi) and 50°C, then cooled and filtered. The filtrate was combined with an IMS wash (50ml) of the filter pad and concentrated under reduced pressure to a colume of 100ml. The remaining ethanol was removed by distillation, and replaced with ethyl acetate until a head temperature of 77°C had been achieved. The cooled mixture was granulated at 4°C, filtered and dried to afford the title compound (13.17g, 73%) as a light brown solid. δ ($DMSO_{d6}$): 0.90 (3H,t), 2.54 (2H,q), 4.48 (2H,s), 5.31 (2H,s), 6.89 (1H,d), 6.95 (1H,s), 7.11 (1H, s), 7.28 (1H,m), 7.74 (1H,m), 8.50 (1H,d). LRMS: m/z 246 $(M+1)^+$.

(4g) 2-Chloro-5-(4-ethyl-1-piperazinylsulphonyl)benzoic acid (Compound VIIB, X=Cl)

[0061] 2-Chloro-5-chlorosulphonylbenzoic acid (51.02g, 0.2mol) from example (2a) in water was cooled to 5ºC. The pH of the reaction was adjusted to 2.2 using aqueous sodium hydroxide (5M), N-ethylpiperazine was added and the pH adjustment continued to 5.5. The reaction mixture was stirred for 12 hours at ambient temperature. The precipitated solid filtered to afford the title compound. Recrystallisation of the title compound from acetone: water affords a solid with m.p. 267-269ºC. δ (DMSO): 1.00 (3H, s). 2.50 (2H, m), 2.60 (4H, m), 3.00 (4H, m), 7.75 (2H, s), 7.95 (1H, s), m/z (Found: 333 $[M+H]^+$, 100% $C_{13}H_{18}ClN_2O_4S$ requires 333).

(4h) 4-[2-Chloro-5-(4-ethyl-1-piperazinylsulphonyl)benzamido]-5-ethyl-1-(2-pyridylmethyl)-1H-pyrazole-3-carboxamide. (Compound IIB, X=Cl)

[0062] 4-Amino-5-ethyl-1-(2-pyridylmethyl)-1H-pyrazole-3-carboxamide (compound IXB) (4.02g, 16.4mmol) was added to a suspension of 2-chloro-5-(4-ethyl-1-piperazinylsulphonyl)benzoic acid (5.0g,16.4mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (3.15g, 16.4mmol) and 1-hydroxybenzotriazole (2.22g, 16.4mmol) in dichloromethane (50ml). The reaction was stirred for 48 hours at ambient temperature. The reaction mixture was filtered and the solid dried to afford the title compound (2.26g, 24.7%) as a white solid m.p. 185°C. Found: C, 53.26; H, 5.38; N,17.13. $C_{25}H_{30}ClN_7O_4S$ requires C, 53.61; H, 5.40; N, 17.51. δ (DMSO) : 0.90 (3H, t), 1.20 (3H, t), 2.30 (2H, q), 2.21 (4H, m), 2.70 (2H, q), 2.95 (4H, m), 5.50 (2H, s), 7.10 (1H, d), 7.20 (1H, m), 7.30 (2H, m), 7.85 (3H, m), 7.93 (1H, s), 8.55 (1H, d), 9.92 (1H, s). m/z (Found: 560.1835 ($[M+H]^+$, 65%). $C_{25}H_{31}ClN_7O_4S$ requires 560.184677).

(4i) 1-Ethyl-4-{3-[3-ethyl-6,7-dihydro-7-oxo-2-(2-pyridylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenylsulphonyl}piperazine. (Compound IB)

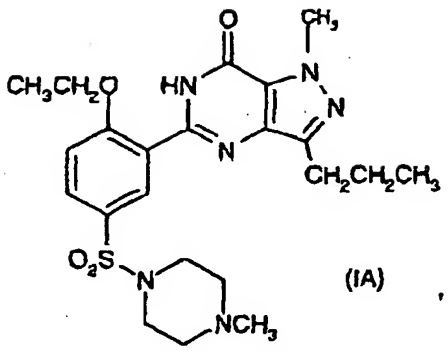
[0063] Potassium *t*-butoxide (0.90g, 8.02mmol) was added to a suspension of the title compound of example 4(h) (1.5g, 2.68mmol) in propan-1-ol (10ml) and the mixture was heated under reflux for 48 hours. The reaction mixture was cooled and the precipitated solid was filtered and dried to afford the title compound (1.16g, 80%). Recrystallisation of the title compound from methyl isobutyl ketone afforded a solid with m.p. 95°C. δ ($CDCl_3$): 1.00 (3H, t), 1.12 (3H, t), 1.30 (3H, t), 2.02 (2H, m), 2.40 (2H, q), 2.50 (4H, m), 3.10 (6H, m), 4.13 (2H, t), 5.70 (2H, s), 7.20 (3H, m), 7.60 (1H, m), 7.80 (1H, m), 8.55 (1H, m), 8.80 (1H, m), 10.60 (1H, s). m/z (Found: 566.257068 ($[M+H]^+$, 100%). $C_{28}H_{36}N_7O_4S$. requires 566.257068).

[0064] On sampling the reaction mixture using HPLC, the result suggests that the reaction pathway proceeds mainly via intermediate IVB.

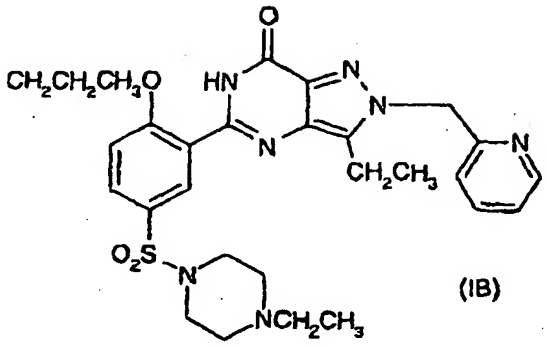
The invention thus provides an excellent process for preparing compounds of formula I which is safe (obviates the need to use carcinogenic alkylating reagents), is economic, utilises readily available starting materials, and which combines a novel displacement and ring closure reaction in one reaction vessel.

Claims

1. A process for the preparation of a compound of formulae (IA) and (IB)

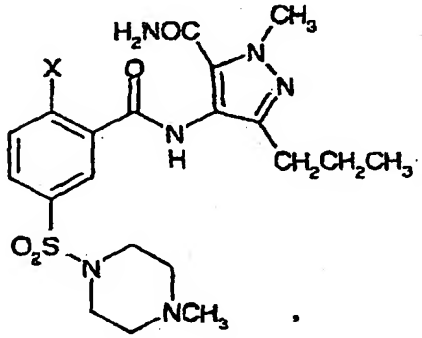


(IA)

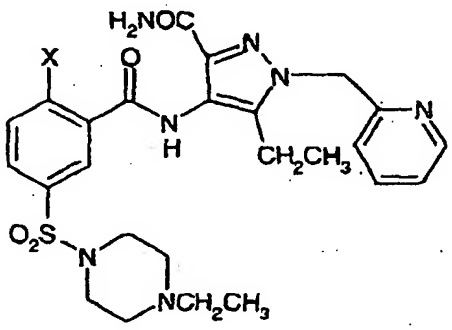


(IB)

comprising reacting a compound of formula (IIA) and (IIB) respectively



(IIA)



(IIB)

in the presence of ^-OR, wherein R in the case of formation of compound (IA) is CH_2CH_3 and R in the case of formation of compound (IB) is $CH_2CH_2CH_3$, wherein X is a leaving group selected from the group consisting of optionally substituted arylsulphonyloxy, C_1-C_4 alkylsulphonyloxy, nitro or halo substituted benzenesulphonyloxy, C_1-C_4 perfluoroalkylsulphonyloxy, optionally substituted aroyloxy, C_1-C_4 perfluoroalkanoyloxy, C_1-C_4 alkanoyloxy, halo, diazonium, methoxy, oxonium, perchloryloxy, quaternaryammonium C_1-C_4 alkylsulphonyloxy, halosulphonyloxy, halonium and diarylsulphonylamino.

2. A process as claimed in claim 1 wherein X is a halo or methoxy.

3. A process as claimed in claim 2 wherein X is fluoro, chloro or methoxy.

4. A process as claimed in claim 3 wherein X is fluoro or chloro.

5. A process as claimed in any one of the preceding claims wherein ^-OR is present with an auxiliary base.

6. A process as claimed in claim 5 wherein the auxiliary base is selected from the group consisting of sterically hindered base, metal salts of 1-methyl piperazine (especially for compound IA), 1-ethylpiperazine (especially for compound IB), morpholine, a metal hydride, metal oxide, metal carbonate and metal bicarbonate.

7. A process as claimed in claim 6 wherein the sterically hindered base is a metal salt of a sterically hindered alcohol or amine.

8. A process as claimed in claim 7 wherein the metal salt of a sterically hindered alcohol or amine is selected from the group consisting of a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol and a secondary or tertiary (C_3-C_8 cycloalkyl)C_1-C_6 alkanol, a N-(secondary or tertiary C_3-C_6 alkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a N-(C_3-C_8 cycloalkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a di(C_3-C_8 cycloalkyl)

amine or hexamethyldisilazane, 1,5-diazabicyclo[4,3,0]non-5-ene 1,8-diazabicyclo[5,4,0]undec-7-ene and tertiary amines such as triethylamine.

9. A process as claimed in claim 8 wherein the auxiliary base is a metal salt of a tertiary alkanol.

10. A process as claimed in any one of the preceding claims wherein the reaction is carried out in an inert solvent or ROH or a mixture of both.

11. A process as claimed in claim 10 wherein the solvent is selected from the group consisting of ethanol (for IA), n-propanol (for IB), a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a tertiary C_4-C_{12} cycloalkanol, a secondary or tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine, and mixtures thereof.

12. A process as claimed in claim 11 wherein the solvent is selected from the group consisting of ethanol (for IA), n-propanol (for IB), a tertiary C_4-C_{12} alkanol, a tertiary C_4-C_{12} cycloalkanol, a tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine, and mixtures thereof.

13. A process as claimed in claim 12 wherein the solvent is ethanol (for IA) or propanol (for IB).

14. A process for the preparation of a compound of formula (IA) and (IB) according to any one of the preceding claims comprising reacting a compound of formula (IIA) and (IIB) respectively with ZOR, or with ROH and an auxiliary base as defined hereinbefore or with ZOR and an auxiliary base, wherein ZOR is a salt of OR and Z is a cation.

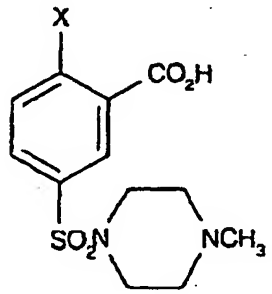
15. A process as claimed in claim 14 wherein compound (IA) is formed by reaction of compound (IIA):

a) with ethanol and auxiliary base, optionally in an inert solvent; or
b) with ZOEt and an auxiliary base in ethanol or an inert solvent or both; or)
c) with ZOEt and ethanol or an inert solvent or both.

16. A process as claimed in claim 14 wherein compound (IB) is formed by reaction of compound (IIB):

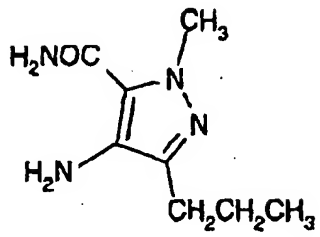
d) with propanol and auxiliary base, optionally in an inert solvent (as defined herebefore); or
e) with ZOPr and an auxiliary base, in propanol or an inert solvent or both; or
f) with ZOPr, and propanol or an inert solvent or both.

17. A process as claimed in any one of the preceding claims wherein the compound of formula (IIA) is prepared by coupling a compound of formula (VIIA)



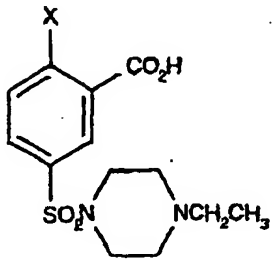
(VIIA)

with a compound of formula (IXA)



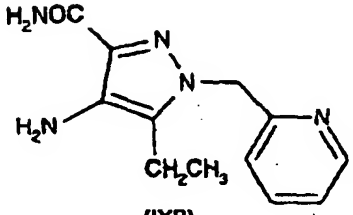
(IXA)

and a compound of formula (IIB) is prepared by coupling a compound of formula (VIIB)



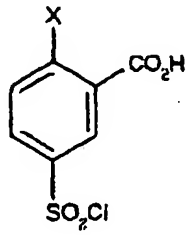
(VIIB)

with a compound of formula (IXB)



(IXB)

18. A process as claimed in claim 17 wherein a compound of the formula (VIIA) is formed by coupling a compound of formula (VIA) with N-methylpiperazine



(VIA) ;

and a compound of formula (VIIB) is formed by coupling a compound of formula (VIA) with N-ethylpiperazine.

19. A process for the preparation of a compound of formula (IA) according to the process of any one of claims 1 to 15, 17 and 18.

20. A process for the preparation of a compound of formula (IA) as defined in claim 1 comprising:

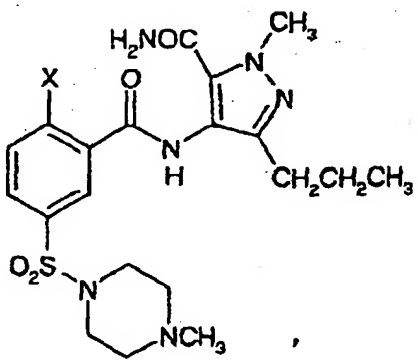
(a) coupling a compound of formula (VIIA) as defined in claim 17, wherein X is as defined in claim 1, with a compound of formula (IXA) as defined in claim 17 to give a compound of formula (IIA) as defined in claim 1; and
(b) reacting a compound of formula (IIA) in the presence of $^{-}OCH_2CH_3$ to give the compound of formula (IA).

21. A process for the preparation of a compound of formula (IA) as defined in claim 1 comprising:

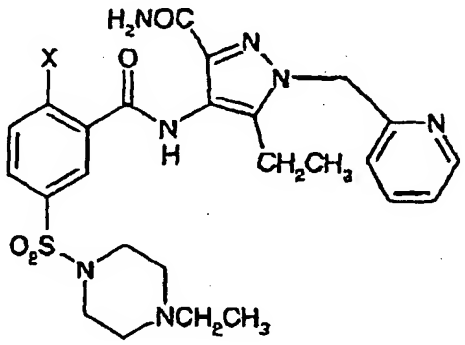
(a) coupling a compound of formula (VIA) as defined in claim 18, wherein X is as defined in claim 1, with N-methylpiperazine, to form a compound of formula (VIIA) as defined in claim 17, wherein X is as defined in claim 1;
(b) coupling a compound of formula (VIIA) with a compound of formula (IXA) as defined in claim 17 to give a compound of formula (IIA)as defined in claim 1; and
(c) reacting a compound of formula (IIA) in the presence of $^{-}OCH_2CH_3$ to give the compound of formula (IA).

22. A process according to either claim 20 or 21 further comprising the process features of any one of claims 2 to 15.

23. A compound of formula (IIA) and (IIB):



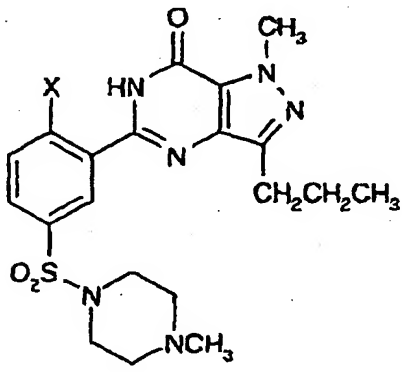
(IIA)



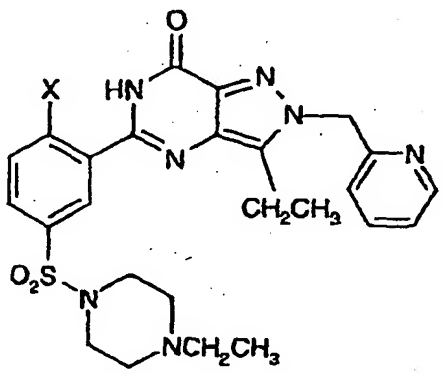
(IIB)

wherein X is as defined in any one of claims 1 to 4.

24. A compound of formula (IIIA) and (IIIB):



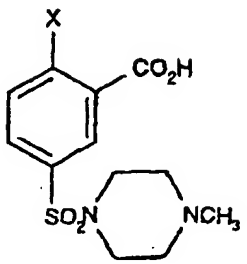
(IIIA)



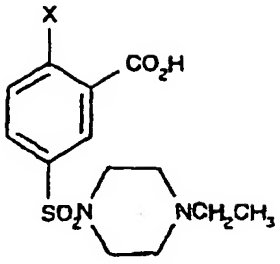
(IIIB)

wherein X is as defined in anyone of claims 1 to 4.

25. A compound of formula (VIIA) and (VIIB)



(VIIA)



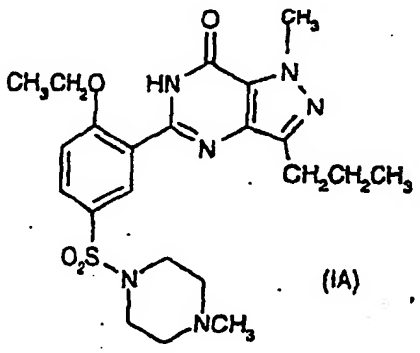
(VIIB)

wherein X is as defined in anyone of claims 1 to 4.

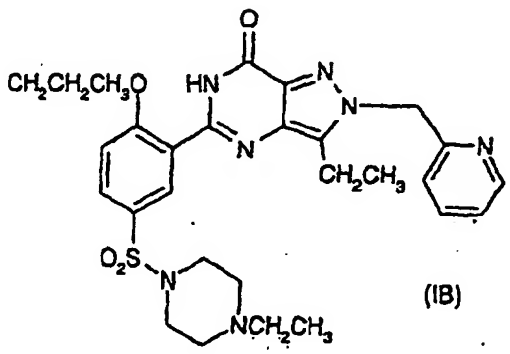
26. A compound as claimed in any of claims 23 to 25 wherein X is selected from the group consisting of fluoro, chloro and methoxy.

Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formeln (IA) und (IB)

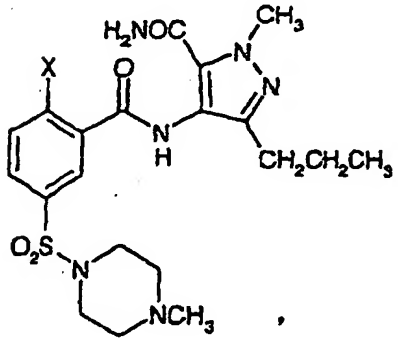


(IA)

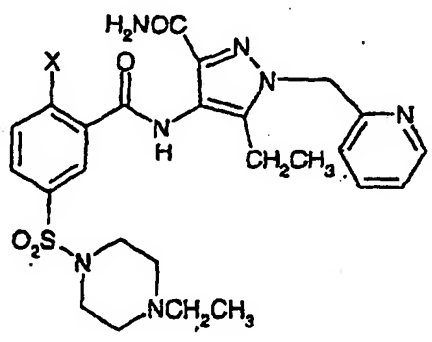


(IB)

umfassend die Umsetzen einer Verbindung der Formel (IIA) bzw. (IIB)



(IIA)



(IIB)

in Gegenwart von ^-OR, worin R im Falle der Bildung der Verbindung (IA) CH_2CH_3 bedeutet und R im Falle der Bildung der Verbindung (IB) $CH_2CH_2CH_3$ bedeutet, wobei X eine Abgangsgruppe bedeutet, die aus der aus optional substituiertem Arylsulfonyloxy, C_1-C_4-Alkylsulfonyloxy, nitro- oder halogensubstituiertem Benzolsulfonyloxy, C_1-C_4-Perfluoralkylsulfonyloxy, optional substituiertem Aroyloxy, C_1-C_4-Perfluoralkanoyloxy, C_1-C_4-Alkanoyloxy, Halogen, Diazonium, Methoxy, Oxonium, Perchloryloxy, quaternäres-Ammonium- C_1-C_4alkylsulfonyloxy, Halogensulfonyloxy, Halonium und Diarylsulfonylamino bestehenden Gruppe ausgewählt ist.

2. Verfahren gemäß Anspruch 1, wobei X ein Halogen oder Methoxy bedeutet.

3. Verfahren gemäß Anspruch 2, wobei X Fluor, Chlor oder Methoxy bedeutet.

4. Verfahren gemäß Anspruch 3, wobei X Fluor oder Chlor bedeutet.

5. Verfahren gemäß einem der vorhergehenden Ansprüche, wobei ^-OR mit einer Hilfsbase vorhanden ist.

6. Verfahren gemäß Anspruch 5, wobei die Hilfsbase aus der aus einer sterisch gehinderten Base, Metallsalzen von 1-Methylpiperazin (insbesondere für die Verbindung IA), 1-Ethylpiperazin (insbesondere für die Verbindung IB), Morpholin, einem Metallhydrid, Metalloxid, Metallcarbonat und Metallbicarbonat bestehenden Gruppe ausgewählt ist.

7. Verfahren gemäß Anspruch 6, wobei die sterisch gehinderte Base ein Metallsalz eines sterisch gehinderten Alkohols oder Amins ist.

8. Verfahren gemäß Anspruch 7, wobei das Metallsalz eines sterisch gehinderten Alkohols oder Amins aus der aus einem sekundären oder tertiären C_4-C_{12}-Alkanol, einem C_3-C_{12}-Cycloalkanol und einem sekundären oder tertiären (C_3-C_8-Cycloalkyl)-C_1-C_6-alkanol, einem N-(sekundäres oder tertiäres C_3-C_6-Alkyl)-N-(primäres, sekundäres oder tertiäres C_3-C_6-alkyl)amin, einem N-(C_3-C_8-Cycloalkyl)-N-(primäres, sekundäres oder tertiäres C_3-C_6-alkyl)amin, einem Di(C_3-C_8-cycloalkyl)amin oder Hexamethyldisilazan, 1,5-Diazabicyclo[4,3,0]non-5-en, 1,8-Diazabicyclo [5,4,0]undec-7-en und tertiären Aminen, wie Triethylamin, bestehenden Gruppe ausgewählt ist.

9. Verfahren gemäß Anspruch 8, wobei die Hilfsbase ein Metallsalz eines tertiären Alkanols ist.

10. Verfahren gemäß einem der vorhergehenden Ansprüche, wobei die Reaktion in einem inerten Lösemittel oder ROH oder einem Gemisch von beiden durchgeführt wird.

11. Verfahren gemäß Anspruch 10, wobei das Lösemittel aus der aus Ethanol (für IA), n-Propanol (für IB), einem sekundären oder tertiären C_4-C_{12}-Alkanol, einem C_3-C_{12}-Cycloalkanol, einem tertiären C_4-C_{12}-Cycloalkanol, einem sekundären oder tertiären (C_3-C_7-Cycloalkyl)-C_2-C_6-alkanol, einem C_3-C_9-Alkanon, 1,2-Dimethoxyethan, 1,2-Diethoxyethan, Diglyme, Tetrahydrofuran, 1,4-Dioxan, Toluol, Xylol, Chlorbenzol, 1,2-Dichlorbenzol, Acetonitril, Dimethylsulfoxid, Sulfolan, Dimethylformamid, N-Methylpyrrolidin-2-on, Pyridin und Gemischen derselben bestehenden Gruppe ausgewählt ist.

12. Verfahren gemäß Anspruch 11, wobei das Lösemittel aus der aus Ethanol (für IA), n-Propanol (für IB), einem tertiären C_4-C_{12}-Alkanol, einem tertiären C_4-C_{12}-Cycloalkanol, einem tertiären (C_3-C_7-Cycloalkyl)-C_2-C_6-alkanol, einem C_3-C_9-Alkanon, 1,2-Dimethoxyethan, 1,2-Diethoxyethan, Diglyme, Tetrahydrofuran, 1,4-Dioxan, Toluol, Xylol, Chlorbenzol, 1,2-Dichlorbenzol, Acetonitril, Sulfolan, Dimethylformamid, N-Methylpyrrolidin-2-on, Pyridin und Gemischen derselben bestehenden Gruppe ausgewählt ist.

13. Verfahren gemäß Anspruch 12, wobei das Lösemittel Ethanol (für IA) oder Propanol (für IB) ist.

14. Verfahren zur Herstellung einer Verbindung der Formel (IA) und (IB) gemäß einem der vorhergehenden Ansprüche, das das Umsetzen einer Verbindung der Formel (IIA) bzw. (IIB) mit ZOR oder mit ROH und einer wie im Vorhergehenden definierten Hilfsbase oder mit ZOR und einer Hilfsbase umfasst, wobei ZOR ein Salz von OR bedeutet und Z ein Kation bedeutet.

15. Verfahren gemäß Anspruch 14, wobei die Verbindung (IA) durch Umsetzung der Verbindung (IIA):

a) mit Ethanol und einer Hilfsbase, optional in einem inerten Lösemittel; oder

b) mit ZOEt und einer Hilfsbase in Ethanol oder einem inerten Lösemittel oder beiden; oder
c) mit ZOEt und Ethanol oder einem inerten Lösemittel oder beiden

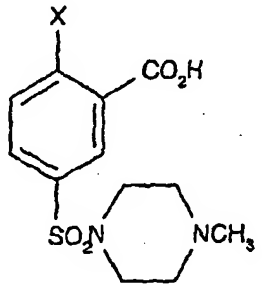
gebildet wird.

16. Verfahren gemäß Anspruch 14, wobei die Verbindung (IB) durch Umsetzung der Verbindung (IIB):

d) mit Propanol und einer Hilfsbase, optional in einem (wie im Vorhergehenden definierten) inerten Lösemittel; oder
e) mit ZOPr und einer Hilfsbase in Propanol oder einem inerten Lösemittel oder beiden; oder
f) mit ZOPr und Propanol oder einem inerten Lösemittel oder beiden

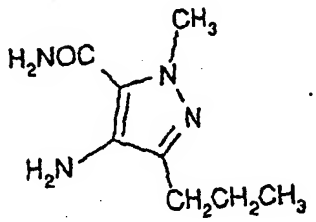
gebildet wird.

17. Verfahren gemäß einem der vorhergehenden Ansprüche, wobei die Verbindung der Formel (IIA) durch Koppeln einer Verbindung der Formel (VIIA)



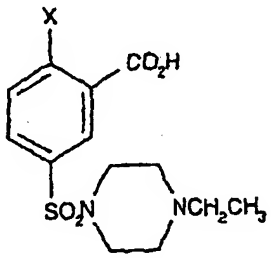
(VIIA)

mit einer Verbindung der Formel (IXA)



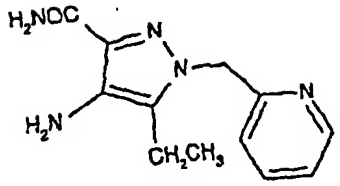
(IXA)

hergestellt wird und eine Verbindung der Formel (IIB) durch Koppeln einer Verbindung der Formel (VIIB)



(VIIB)

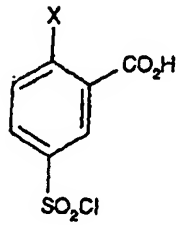
mit einer Verbindung der Formel (IXB)



(IXB)

hergestellt wird.

18. Verfahren gemäß Anspruch 17, wobei eine Verbindung der Formel (VIIA) durch Koppeln einer Verbindung der Formel (VIA) mit N-Methylpiperazin



(VIA)

gebildet wird und eine Verbindung der Formel (VIIB) durch Koppeln einer Verbindung der Formel (VIA) mit N-Ethylpiperazin gebildet wird.

19. Verfahren zur Herstellung einer Verbindung der Formel (IA) gemäß dem Verfahren von einem der Ansprüche 1 bis 15, 17 und 18.

20. Verfahren zur Herstellung einer Verbindung der Formel (IA) gemäß der Definition in Anspruch 1, das umfasst:

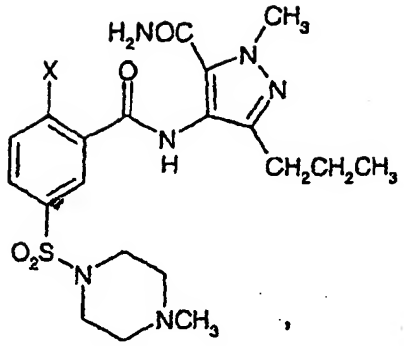
(a) Koppeln einer Verbindung der Formel (VIIA) gemäß der Definition in Anspruch 17, worin X wie in Anspruch 1 definiert ist, mit einer Verbindung der Formel (IXA) gemäß der Definition in Anspruch 17 unter Bildung einer Verbindung der Formel (IIA) gemäß der Definition in Anspruch 1; und
(b) Umsetzen einer Verbindung der Formel (IIA) in Gegenwart von $^{-}OCH_2CH_3$ unter Bildung der Verbindung der Formel (IA).

21. Verfahren zur Herstellung einer Verbindung der Formel (IA) gemäß der Definition in Anspruch 1, das umfasst:

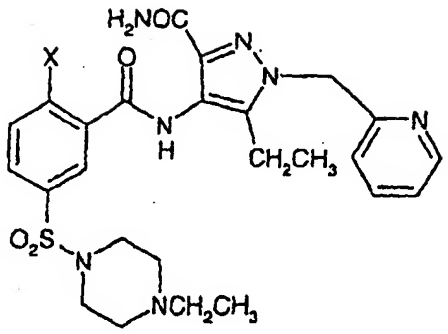
(a) Koppeln einer Verbindung der Formel (VIA) gemäß der Definition in Anspruch 18, worin X wie in Anspruch 1 definiert ist, mit N-Methylpiperazin unter Bildung einer Verbindung der Formel (VIIA) gemäß der Definition in Anspruch 17, worin X wie in Anspruch 1 definiert ist;
(b) Koppeln einer Verbindung der Formel (VIIA) mit einer Verbindung der Formel (IXA) gemäß der Definition in Anspruch 17 unter Bildung einer Verbindung der Formel (IIA) gemäß der Definition in Anspruch 1; und
(c) Umsetzen einer Verbindung der Formel (IIA) in Gegenwart von $^{-}OCH_2CH_3$ unter Bildung der Verbindung der Formel (IA).

22. Verfahren gemäß entweder Anspruch 20 oder 21, das ferner die Verfahrensmerkmale von einem der Ansprüche 2 bis 15 umfasst.

23. Verbindung der Formel (IIA) und (IIB):



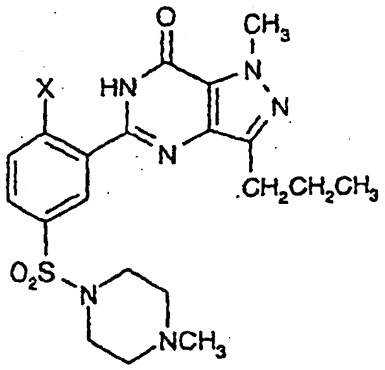
(IIA)



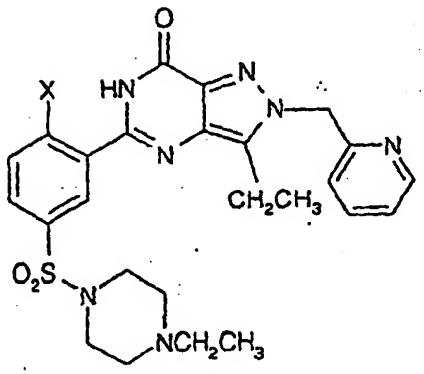
(IIB)

worin X wie in einem der Ansprüche 1 bis 4 definiert ist.

24. Verbindung der Formel (IIIA) und (IIIB):



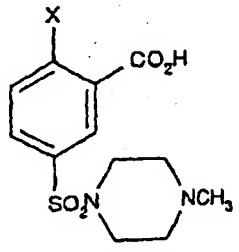
(IIIA)



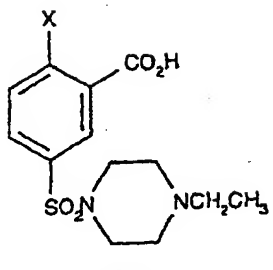
(IIIB)

worin X wie in einem der Ansprüche 1 bis 4 definiert ist.

25. Verbindung der Formel (VIIA) und (VIIB):



(VIIA)



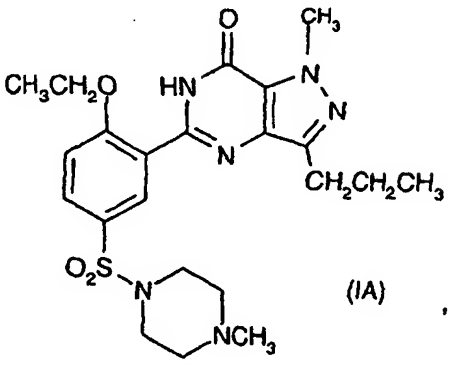
(VIIB)

worin X wie in einem der Ansprüche 1 bis 4 definiert ist.

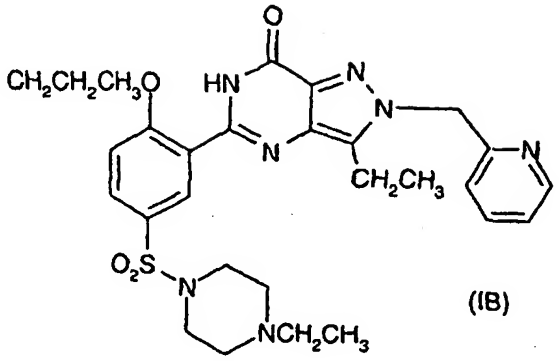
26. Verbindung gemäß einem der Ansprüche 23 bis 25, worin X aus der aus Fluor, Chlor und Methoxy bestehenden Gruppe ausgewählt ist.

Revendications

1. Procédé de préparation d'un composé de formule (IA) et (IB)

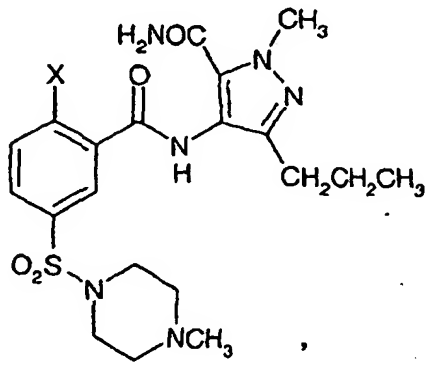


(IA)

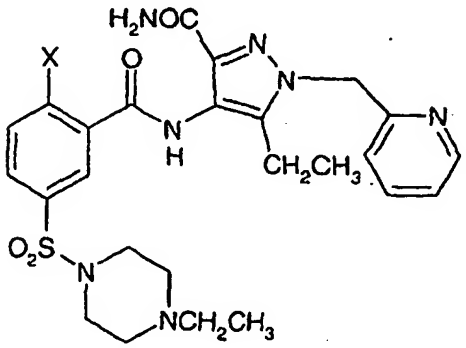


(IB)

comprenant les étapes de réaction d'un composé de formule (IIA) et (IIB) respectivement



(IIA)



(IIB)

en présence de OR, dans lequel R dans le cas de la formation du composé (IA) est CH_2CH_3 et R dans le cas de la formation du composé (IB) est $CH_2CH_2CH_3$, X étant un groupe partant choisi dans le groupe constitué par les groupes arylsulfonyloxy éventuellement substitués, alkylsulfonyloxy en C_1-C_4, benzènesulfonyloxy substitué par un groupe nitro ou un halogène, perfluoroalkylsulfonyloxy en C_1-C_4, aroyloxy éventuellement substitués, perfluoroalcanoyloxy en C_1-C_4, alcanoyloxy en C_1-C_4, les halogènes, l'ion diazonium, le groupe méthoxy, l'ion oxonium, les groupes perchloryloxy, ammonium quaternaire-alkylsulfonyloxy en C_1-C_4, halogénosulfonyloxy, les ions halonium et les groupes diarylsulfonylamino.

2. Procédé selon la revendication 1 dans lequel X est un halogène ou un groupe méthoxy.

3. Procédé selon la revendication 2 dans lequel X est un fluor, un chlore ou un groupe méthoxy.

4. Procédé selon la revendication 3 dans lequel X est un fluor ou un chlore.

5. Procédé selon l'une quelconque des revendications précédentes dans lequel OR est présent avec une base auxiliaire.

6. Procédé selon la revendication 5 dans lequel la base auxiliaire est choisie dans le groupe constitué par les bases stériquement encombrées, les sels métalliques de 1-méthylpipérazine (en particulier pour le composé IA), de 1-éthylpipérazine (en particulier pour le composé IB), la morpholine, les hydrures métalliques, les oxydes métalliques, les carbonates métalliques et les bicarbonates métalliques.

7. Procédé selon la revendication 6 dans lequel la base stériquement encombrée est un sel métallique d'un alcool ou d'une amine stériquement encombré.

8. Procédé selon la revendication 7 dans lequel le sel métallique d'un alcool ou d'une amine stériquement encombré est choisi dans le groupe constitué par les alcools en C_4-C_{12} secondaires ou tertiaires, les alcools cycliques en C_3-C_{12}, les (cycloalkyl en C_3-C_8)alcools en C_1-C_6 secondaires ou tertiaires, les N-(alkyl en C_3-C_6 secondaire ou tertiaire)-N-(alkyl en C_3-C_6 primaire, secondaire ou tertiaire)amines, les N-(cycloalkyl en C_3-C_8)-N-(alkyl en C_3-C_6 primaire, secondaire ou tertiaire)amines, les di(cycloalkyl en C_3-C_8)amines, l'hexaméthyldisilazane, le 1,5-diazabicyclo[4,3,0]non-5-ène, le 1,8-diazabicyclo[5,4,0]undéc-7-ène et les amines tertiaires telles que la triéthylamine.

9. Procédé selon la revendication 8 dans lequel la base auxiliaire est un sel métallique d'un alcool tertiaire.

10. Procédé selon l'une quelconque des revendications précédentes dans lequel la réaction est réalisée dans un solvant inerte ou ROH ou un mélange des deux.

11. Procédé selon la revendication 10 dans lequel le solvant est choisi dans le groupe constitué par l'éthanol (pour IA), le n-propanol (pour IB), les alcools en C_4-C_{12} secondaires ou tertiaires, les alcools cycliques en C_3-C_{12}, les alcools cycliques en C_4-C_{12} tertiaires, les (cycloalkyl en C_3-C_7)alcools en C_2-C_6 secondaires ou tertiaires, les cétones en C_3-C_9, le 1,2-diméthoxyéthane, le 1,2-diéthoxyéthane, le diglyme, le tétrahydrofurane, le 1,4-dioxane, le toluène, le xylène, le chlorobenzène, le 1,2-dichlorobenzène, l'acétonitrile, le diméthylsulfoxyde, le sulfolane, le diméthylformamide, la N-méthylpyrrolidin-2-one, la pyridine, et les mélanges de ceux-ci.

12. Procédé selon la revendication 11 dans lequel le solvant est choisi dans le groupe constitué par l'éthanol (pour IA), le n-propanol (pour IB), les alcools en C_4-C_{12} tertiaires, les alcools cycliques en C_4-C_{12} tertiaires, les (cycloalkyl en C_3-C_7)alcools en C_2-C_6 tertiaires, les cétones en C_3-C_9, le 1,2-diméthoxyéthane, le 1,2-diéthoxyéthane, le diglyme, le tétrahydrofurane, le 1,4-dioxane, le toluène, le xylène, le chlorobenzène, le 1,2-dichlorobenzène, l'acétonitrile, le sulfolane, le diméthylformamide, la N-méthylpyrrolidin-2-one, la pyridine, et les mélanges de ceux-ci.

13. Procédé selon la revendication 12 dans lequel le solvant est l'éthanol (pour IA) ou le propanol (pour IB).

14. Procédé de préparation d'un composé de formule (IA) et (IB) selon l'une quelconque des revendications précédentes comprenant les étapes de réaction d'un composé de formule (IIA) et (IIB) respectivement avec ZOR, ou avec ROH et une base auxiliaire telle que définie ci-avant, ou avec ZOR et une base auxiliaire, ZOR étant un sel de OR et Z étant un cation.

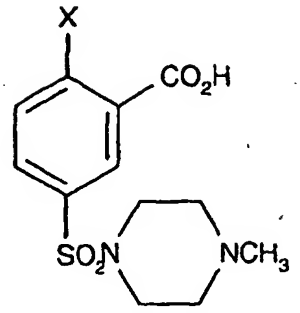
15. Procédé selon la revendication 14 dans lequel le composé (IA) est formé par réaction du composé (IIA) :

    a) avec de l'éthanol et une base auxiliaire, éventuellement dans un solvant inerte ; ou
    b) avec ZOEt et une base auxiliaire, dans de l'éthanol ou un solvant inerte ou les deux ; ou
    c) avec ZOEt et de l'éthanol ou un solvant inerte ou les deux.

16. Procédé selon la revendication 14 dans lequel le composé (IB) est formé par réaction du composé (IIB) :

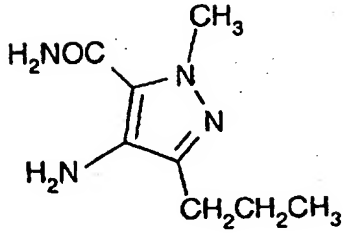
    d) avec du propanol et une base auxiliaire, éventuellement dans un solvant inerte (tel que défini ci-avant) ; ou
    e) avec ZOPr et une base auxiliaire, dans du propanol ou un solvant inerte ou les deux ; ou
    f) avec ZOPr et du propanol ou un solvant inerte ou les deux.

17. Procédé selon l'une quelconque des revendications précédentes dans lequel le composé de formule (IIA) est préparé en couplant un composé de formule (VIIA)



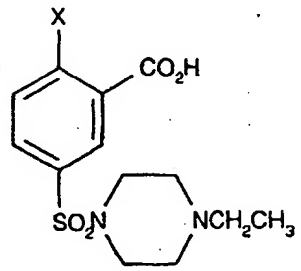
(VIIA)

avec un composé de formule (IXA)



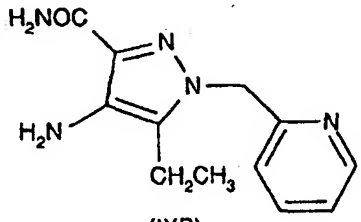
(IXA)

et le composé de formule (IIB) est préparé en couplant un composé de formule (VIIB)



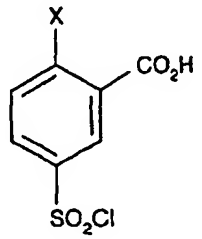
(VIIB)

avec un composé de formule (IXB)



(IXB)

18. Procédé selon la revendication 17 dans lequel le composé de formule (VIIA) est formé en couplant un composé de formule (VIA) avec de la N-méthylpipérazine



(VIA) ;

et le composé de formule (VIIB) est formé en couplant un composé de formule (VIA) avec de la N-éthylpipérazine.

19. Procédé de préparation d'un composé de formule (IA) selon le procédé de l'une quelconque des revendications 1 à 15, 17 et 18.

20. Procédé de préparation d'un composé de formule (IA) tel que défini dans la revendication 1 comprenant les étapes de :

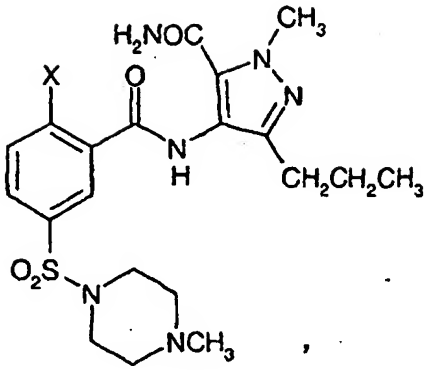
(a) couplage d'un composé de formule (VIIA) tel que défini dans la revendication 17, dans lequel X est tel que défini dans la revendication 1, avec un composé de formule (IXA) tel que défini dans la revendication 17 pour donner un composé de formule (IIA) tel que défini dans la revendication 1 ; et
(b) réaction du composé de formule (IIA) en présence de OCH_2CH_3 pour donner le composé de formule (IA).

21. Procédé de préparation d'un composé de formule (IA) tel que défini dans la revendication 1 comprenant les étapes de:

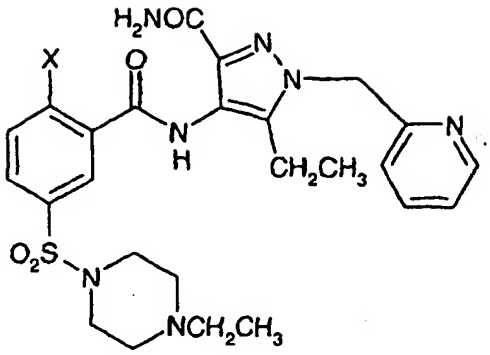
(a) couplage d'un composé de formule (VIA) tel que défini dans la revendication 18, dans lequel X est tel que défini dans la revendication 1, avec de la N-méthylpipérazine, pour former un composé de formule (VIIA) tel que défini dans la revendication 17, dans lequel X est tel que défini dans la revendication 1 ;
(b) couplage du composé de formule (VIIA) avec un composé de formule (IXA) tel que défini dans la revendication 17 pour donner un composé de formule (IIA) tel que défini dans la revendication 1 ; et
(c) réaction du composé de formule (IIA) en présence de OCH_2CH_3 pour donner le composé de formule (IA).

22. Procédé selon l'une ou l'autre des revendications 20 et 21 comprenant en outre les caractéristiques de procédé de l'une quelconque des revendications 2 à 15.

23. Composé de formule (IIA) et (IIB) :



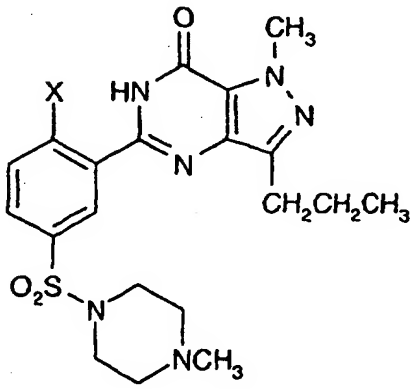
(IIA)



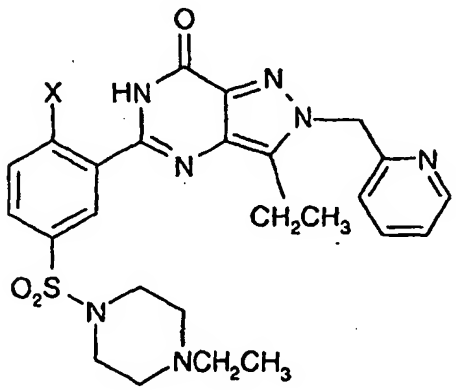
(IIB)

dans lequel X est tel que défini dans l'une quelconque des revendications 1 à 4.

24. Composé de formule (IIIA) et (IIIB) :



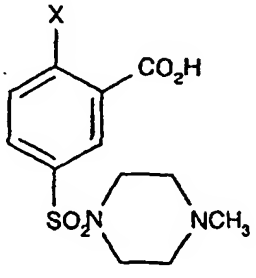
(IIIA)



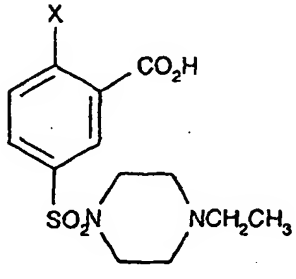
(IIIB)

dans lequel X est tel que défini dans l'une quelconque des revendications 1 à 4.

25. Composé de formule (VIIA) et (VIIB) :



(VIIA)



(VIIB)

dans lequel X est tel que défini dans l'une quelconque des revendications 1 à 4.

26. Composé selon l'une quelconque des revendications 23 à 25 dans lequel X est choisi dans le groupe constitué par le fluor, le chlore et le groupe méthoxy.